REMARKS

Status of the claims

Claims 1-34 and 36-43 are pending and under consideration in this application. All the pending claims stand rejected. After entry of the amendments made herein, claims 1-15, 17-34, and 36-43 will be pending and under consideration in this application, claim 16 having been cancelled. Claims 1,15, 22, 34, and 36 are amended. Support for these amendments can be found throughout the specification, e.g., at page 12, lines 24-31, page 13, lines 23-24, and page 37, lines 11-12. Some of the claims have been amended for purely grammatical purposes (e.g., claim 22) or to correct antecedent bases (e.g., claims 15 and 34). No new matter is added by any of the amendments made herein.

Telephone conversation with Supervisory Examiner Deborah Reynolds

After several attempts to contact Examiner Sorbello by telephone in order to schedule a telephone interview, Applicants' undersigned representative learned in a telephone conversation with Supervisory Examiner Deborah Reynolds that Examiner Sorbello was no longer employed at the U.S. Patent and Trademark Office (USPTO). Supervisory Examiner Reynolds requested that, prior to a telephone interview, Applicants submit a response to the final Office Action in order for a new Examiner assigned to the case to obtain an understanding of the case and its status. While Applicants' undersigned representative indicated that this would be an inconvenience to the clients since they are private individuals who did not want to incur more expenses than absolutely necessary, he agreed to submit such a response. This is that response. In light of these considerations, Applicants respectfully request that the amendments and remarks herein be entered and considered by the new Examiner. Furthermore, Applicants respectfully request that, after considering these amendments and remarks, the new Examiner contact Applicants' undersigned representative at the telephone number listed below.

Sequence Listing Diskette

As requested on page 2, paragraph 3, of the Office Action and in CRF Problem Report attached to the Office Action, Applicants enclose herewith a replacement diskette containing the Sequence Listing for the instant application.

35 U.S.C. §112, second paragraph, rejection

The rejection of claim 34 for lacking antecedent basis is maintained.

The above amendment to claim 34 renders this rejection moot and thus Applicants respectfully request that it be withdrawn.

35 U.S.C. §112, first paragraph, rejections

(a) Claims 1-34 and 36-43 stand rejected on the grounds that the specification allegedly does not reasonably provide enablement for the claims. Applicants respectfully traverse this rejection.

With respect to the remarks on page 3, line 16, page 5, line 15, of the Office Action, Applicants understand the prior Examiner's position to be that the claims do not require the targeting cell to be isolated and the methods of treatment to be *ex vivo*, and thus that Applicants' reference to publications (cited by the prior Examiner) as pointing to the efficacy of *ex vivo* treatments is not relevant. However, the above amendments to claims 1, 22, and 36 make it very clear that the methods of the invention are indeed *ex vivo*. Moreover with respect to the prior Examiner's concern that any targeting cell is covered by the claims (Office Action, page 4, lines 1-2), Applicants have limited the targeting cells to T lymphocytes.

The prior Examiner acknowledged that several targeting and toxic domains are enabled (Office Action, page 3, lines 7-8). These domains were shown in actual experiments to be functional. However enablement of a genus does not require that all embodiments of a claimed invention be proved functional by actual experimentation. Applicants respectfully submit that given the teaching of the specification and the state of the art at the priority date of the instant application, one of skill in the art would expect

that a wide range of molecules (e.g., those disclosed in the specification at, for example, pages 19-24) would be functional.

Applicants submit in addition that, given the teaching of the specification and the state of the art at the priority date of the instant application, choosing an appropriate targeting T cell, an appropriate toxic domain, and an appropriate targeting domain for any particular pathogenic cell disease would be entirely routine for one skilled in the art. The Examiner is reminded that

> a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable guidance with respect to the direction in which experimentation should proceed. *In re Wands*, 858 F.2d 731, 736-7 (Fed. Cir. 1988).

With respect to the prior Examiner's comments on page 5, line 16, to page 6, line 10, of the Office Action, Applicants point out that their purpose in citing examples of clinical successes in treating a wide variety of pathogenic cell diseases with immunotoxic molecules *per se* (rather than with targeting cells producing immunotoxic molecules) was to show that, provided a sufficiently high amount of immunotoxic molecules is delivered to relevant pathogenic cells, the immunotoxic molecules can be effective in treating the appropriate pathogenic cell diseases. In addition, given the teaching of the specification and prior art, in particular references such as those cited by the prior Examiner and referred to above in support of the efficacy of *ex vivo* treatments, one of skill in the art would expect that *ex vivo* versions of the "immunotoxic molecule *per se*" methods could be developed that would be at least as effective and almost certainly less toxic to the relevant subjects. This is because one of the problems in using an immunotoxic molecule *per se* approach is that it is difficult to obtain a sufficiently high concentration of the immunotoxic molecule in the region of the pathogenic cell without causing excessive toxicity to neighboring tissue or systemic toxicity. The targeting cell approach solves this problem.

(b) Claims 1-34 and 36-43 stand rejected as allegedly containing subject matter that was not described in the specification so as to reasonably convey to one skilled in the relevant

art at the time the application was filed that Applicants had possession of the claimed invention. Applicants respectfully traverse this rejection.

The comments on page 6, line 17, to page 7, line 8, of the Office Action, indicate the prior Examiner's previously expressed belief that, in order to satisfy the written description requirement, it is necessary that the specification provide the nucleotide sequences of the coding sequences for every fusion protein covered by the instant specification. Applicants respectfully submit that this has never been required, either prior to or subsequent to publication of the new USPTO written description guidelines, for either fusion proteins formed between known polypeptides or even novel polypeptides. Applicants provided in the Response submitted February 14, 2002, examples of issued U.S. patents claiming such proteins and nucleic acids encoding the proteins in the absence of relevant sequence information.

With respect to the prior Examiner's comments on page 7, lines 5-6, of the Office Action, Applicants submit that given the issue date (January 29, 2002) of U.S. Patent No. 6,342,345, prosecution of the relevant application was clearly at least on-going at the time the currently used written description guidelines came into effect.

With respect to the comment on page 7, lines 13-15, Applicants repeat that, as indicated on page 17, lines 28-30, of the specification, linker sequences are not required in the fusion proteins produced by the targeting cells and encoded by the vectors of the invention. Indeed, as indicated in the Chan et al. (1996) reference cited by the prior Examiner and referred to in the instant specification (e.g., page 39, line 20), an effective immunotoxin composed of an IL-3 targeting domain and a DT390 toxic domain without a linker was produced. Moreover, even though the amino acid sequences of useful linker sequences are known in the art, in addition to the linker specifically referred to in the specification (SEQ ID NO:3), a description of the structural requirements for linkers is provided on pages 18, lines 3-7, of the specification. Furthermore, the Chan et al. (1995) reference cited by the prior Examiner and also referred to in the instant specification (e.g., page 38, lines 28-29) provided the amino acid sequence of another useful linker sequence (page 2735, column 1, paragraph 4).

With respect to the comment on page 7, lines 15-17, of the Office Action, Applicants respectfully submit that there were multiple known "fusion proteins that have

the properties of binding affinity to a pathogenic cell" at the priority date of the instant application. Such fusion proteins are described in both the references cited by the prior Examiner and those provided by Applicants as attachments to the Response filed March 27, 2002.

In light of the above considerations, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

35 U.S.C. §103(a) rejection

Claims 1-33 and 36-43 stand rejected as allegedly being unpatentable over Chan at el. (Blood 86:2732-2740, 1995 ("Chan et al. a"); and Blood 88:1445-1456, 1996 ("Chan et al. b")) in view of Yang et al. and further in view of Chen et al. Applicants respectfully traverse the rejection.

From the comments on page 9, line 6, to page 10, line 9, of the Office Action, Applicants understand the prior Examiner's position to be that the cited art contains the requisite motivation to combine its disclosure and thereby render the instant invention obvious. Applicants respectfully disagree with this position.

Applicants emphasize that their arguments against obviousness are essentially "lack of motion to combine" arguments. Thus, in regard to the statement on page 9, lines 17-18 ("However, examiner argues that all the references combined teach all the required elements of the claims"), Applicants submit that the statement in the Response of February 14, 2002, to which the prior Examiner was responding in the above-quoted sentence was made with reference to a lack of motivation to combine and not with respect to any elements of the instant claims that may have been disclosed by the various references.

As pointed out in the Response filed February 14, 2002, the two Chan et al. references describe experiments with fusion proteins containing DT390 fused to either GM-CSF or IL-3. No mention or suggestion of the desirability of using targeting cells of any sort, let alone CD8+ CTL (as disclosed in Yang et al. and Chen et al.), to direct expression of a gene encoding an immunotoxic protein to a tumor cell or infected cell is made by either Chan et al. reference.

With respect to the comments on page 9, lines 9-13, of the Office Action, Applicants respectfully submit that Chan et al.a does not teach "targeting cells comprising a murine GM-CSF gene spliced to a truncated form of DT gene encoding a fusion toxin". Applicants submit that the prior Examiner misread the relevant sentence from Chan et al.a. The sentence is in a paragraph at the end of article's Introduction section and summarizes the experimental approach taken in, and the conclusions of, the study described in the article. This sentence reads in relevant part: "We constructed a fusion toxin targeting cells bearing the mGM-CSF receptor (1) to devise a reagent that is potentially useful in destroying the residual myeloid leukemic cells . . ." (emphasis added). Applicants respectfully submit that, by parsing this sentence correctly, the term "a fusion toxin targeting cells bearing the mGM-CSF receptor" means "a fusion toxin that targets cells bearing the mGM-CSF receptor" and can in no way be construed as disclosing recombinant targeting cells transformed with a vector expressing a fusion toxin. The latter interpretation of the term is completely foreclosed by the sentence following that quoted above, and subsequent text of the article describing the experiments performed in the relevant study. Nowhere in the article is there a mention of "targeting cells" (as disclosed in the instant application) or even the desirability of such cells suggested.

Thus neither of the Chan references contains the necessary motivation to combine its disclosure with that of Yang et al. and/or Chen et al. and thereby to render obvious the invention specified by the instant claims.

Yang et al. and Chen et al. describe experiments using CD8+ CTL to target expression of genes encoding immunotoxins using antibody fragments (Fab and single chain Fv, respectively) fused to toxic proteins to HIV- infected cells *in vitro* and tumor cells *in vitro* and *in vivo*, respectively. The two references focus exclusively on the use of antibodies or antibody fragments for use as targeting domains in immunotoxins. There is in neither reference any mention or the suggestion of the desirability of using targeting domains other than antibodies or antibody fragments. Thus, neither Yang et al. nor Chen et al. contains the necessary motivation to combine its disclosure with that of either or both of the Chan et al. references. and thereby to render obvious the invention specified by the instant claims.

Applicants do not understand the prior Examiner's arguments on page 10, lines 4-9, in support of motivation to combine in the cited art. Clarification is respectfully requested.

Applicants submit that, in addition to a lack of motivation in the cited references to combine the disclosures of the references, the instant invention is non-obvious in view of the surprising results showing the therapeutic efficacy of the targeting cells of the invention (see Examples 1 and 6), even when the cells are administered systemically.

In light of the above considerations, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that all of the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a petition for an automatic extension of time and check in payment of the extension of time. Please apply any additional charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 11/4/02

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Version with markings to show changes made

In the claims:

Claim 16 has been cancelled.

Claims 1, 15, 22, 34 and 36 have been amended as follows:

1. (Amended) An isolated targeting cell comprising a vector, said vector comprising a nucleic acid sequence encoding a fusion protein, said fusion protein comprising:

(a) a targeting domain comprising a first member of an affinity pair; and

(b) a toxic domain comprising a toxic molecule,

wherein said targeting cell is a T lymphocyte and has significant binding affinity for a pathogenic cell, said targeting cell expressing and secreting said fusion protein, and said first member binds to a second member of said affinity pair, said second member being expressed on a surface of the pathogenic cell.

15. (Amended) The targeting cell of claim 1, wherein said [targeting cell] T lymphocyte is a CD8+ T lymphocyte.

22. (Amended) An isolated population of cells, wherein each of a substantial number of [said] the cells of [said] the population is [said] the targeting cell of claim 1.

34. (Amended) A method of treating a subject with a pathogenic cell disease, said method comprising administering said cell population of claim [20] 22 to said subject.

36. (Amended) A method of making said cell population of claim 22, the method comprising:

(a) providing an isolated cell preparation wherein each of a substantial number of said cells of said preparation has significant binding affinity for a pathogenic cell; and

(b) transfecting or transducing said cells of said preparation with a vector comprising a DNA sequence encoding a fusion protein including:

(i) a targeting domain comprising a first member of an affinity pair; and

(ii) a toxic domain comprising a toxic molecule,

wherein, after said transfection or said transduction, a significant number of said cells of said preparation express and secrete the fusion protein, and said first member binds to a second member of the affinity pair, said second member being expressed on a surface of said pathogenic cell.

Attorney's Docket No.: 11983-004001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Daniel A. Vallera et al. Art Unit : 1643
Serial No. : 09/579,738 Examiner : Eleanor Sorbello
Filed : May 26, 2000
Title : CELL-MEDIATED TARGETING OF TOXINS TO PATHOGENIC CELLS

BOX SEQUENCE
U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

VERIFIED STATEMENT UNDER 37 CFR §1.821(f)

I, Gina Maldonado, declare that I personally prepared the paper and the computer-readable copy of the Sequence Listing filed herewith for the above-identified application and that the content of both the paper copy filed on February 14, 2002 and the computer-readable copy filed herewith is the same.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202.

November 4, 2002
Date of Deposit

G Maldonado
Signature

Gina Maldonado
Typed or Printed Name of Person Signing Certificate

of The United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/4/02

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Notice to Comply	Application No. 09/579,738	Applicant(s) Vallera
	Examiner Sorbello	Art Unit 1632

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☒ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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